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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,026	07/30/2001	Rosanne M. Crooke	ISPH-0588	1035

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,026	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks, filed January 1, 2004.

Claims 1, 4-10, and 12 have been amended.

Claims 1, 4-10, 12, and 13 are pending in the instant application.

Information Disclosure Statement

In the previous Office Action, filed September 9, 2003, it was noted that the Japanese Abstract listed as reference AD and BQ on PTO form 1449 had not been considered because it is in a foreign language and no translation was provided.

In response, Applicants request reconsideration of the consideration of documents AD and BQ because Applicants contend that a concise explanation of the relevance of document AD was provided in the Information Disclosure Statement, filed March 31, 2003. Applicants also contend that an ***English language*** abstract of document AD was provided as document BQ. This is not found persuasive because an ***English language*** abstract of neither documents AD or BQ were found in the file. The file contains references AD and BQ, both of which are 4 page Japanese documents, without an English language translation, abstract or otherwise. Therefore, until an English language translation of references AD or BQ has been provided, references AD and BQ will not be considered on the merits.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-10, 12 and 13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cases et al. [WO 99/67368] in view of Bennett et al. [U.S. Patent No. 6,613,567] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is maintained** for the reasons of record set forth in the previous Office Action, filed September 9, 2003.

In response to this rejection, Applicants argue that the combination of Cases, Bennett and Fritz does not provide a reasonable expectation of success sufficient to make a *prima facie* case of obviousness of Applicants' claimed invention. Applicants argue that Cases refers to nucleic acid compositions encoding acyl CoA cholesterol acyltransferase-2 (ACAT-2). Applicants further argue that Cases also provides the coding sequence of the human ACAT-2 gene as SEQ ID NO:2. Applicants contend that in the previous Office Action, the Examiner asserted that SEQ ID NO:2 of cases is identical to SEQ ID NO:3 of the instant invention. Applicants note that these sequences are not identical because SEQ ID NO:2 of Cases contains 1509 nucleotides, while SEQ ID NO:3 of the instant invention contains 1569 nucleotides. Applicants further contend that Cases does not teach a compound targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 that hybridizes with an inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40% or antisense oligonucleotides modified as specified by the present instant claims. Applicants also argue that Bennett and Fritz are cited for "generic" teachings but neither are directed to antisense

oligonucleotides targeted to acyl CoA cholesterol acyltransferase-2. Applicants rebut the Examiner's conclusion that the cited art provides an expectation of success in obtaining antisense oligonucleotides capable of inhibition of acyl CoA cholesterol acyltransferase-2 expression by at least 40%. Specifically, Applicants argue that there is no way for anyone of skill in the art to predict whether one may obtain any particular percentage of inhibition by prior knowledge of generic antisense technology, coupled with a known target sequence. Applicants argue that there is nothing in this combination of prior art that suggests such success with acyl CoA cholesterol acyltransferase-2 would be expected. Applicants argue that one of skill might be motivated to "hope for" such a level of success using generic technology, however, nothing in the prior art allows for such an expectation. Applicants contend that only the present invention identifies that antisense oligonucleotides to acyl CoA cholesterol acyltransferase-2 may be provided that inhibit expression by at least 40%. Applicants argue that, "In fact, as evidenced by Tables I and II of the present specification, it is likely that one might look for an antisense sequence to acyl CoA cholesterol acyltransferase-2 and find sequences that do not inhibit at all or that inhibit by considerably less than 40%". Applicants argue that none of the cited art provides any direction to indicate what sequences, if any, may be characterized by such a claimed level of inhibition of acyl CoA cholesterol acyltransferase-2. Applicants argue that Cases provides no direction regarding the level of inhibition of acyl CoA cholesterol acyltransferase-2. Applicants argue that Fritz's discussion of carriers for oligonucleotides is not directed to inhibition levels. Applicants also argue that the results of antisense studies in Bennett, show that only 12 of 39 tested oligonucleotides and 31 of 39 tested oligonucleotides that hybridized to the unrelated gene HER-2, were able to meet that level of inhibition. Applicants argue that the results with HER-2 does

not permit one skill in the able to predict Applicants results with antisense sequences to acyl CoA cholesterol acyltransferase-2, in which 15 of 23 oligonucleotides tested resulted in oligonucleotides meeting the required inhibition level of 40%. Applicants argue that there is no way to predict what target sequences the person of skill in the art would have used to generate such results, and thus no way to predict Applicants results. Applicants argue that Applicants' assignee, which is a company that specializes in antisense technology and uses the latest in bioinformatics programs, have demonstrated repeatedly that one may investigate 80 or more oligonucleotides in attempts to identify a target site permitting inhibition at a specific high level for a specific gene. Applicants contend that one cannot anticipate similar results when one looks at completely different genes. Applicants conclude by arguing that none of the cited references, taken alone or together, teach or suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 (SEQ ID NO: 3), which specifically hybridizes to and inhibits the expression of acyl CoA cholesterol acyltransferase-2 by at least 40%. Applicants also conclude by arguing that the combination of the cited references does not provide any expectation of success of obtaining antisense sequences that are capable of inhibiting expression of acyl CoA cholesterol acyltransferase-2 by at least 40%.

Applicant's arguments have been fully considered, but are not found persuasive. It is noted that in the previous Office Action, the Examiner asserted that SEQ ID NO:2 of Cases is 100% identical to SEQ ID NO:3 of the instant invention. Applicants disagree with this assessment since SEQ ID NO:2 of Cases is 1509 nucleotides in length and SEQ ID NO:3 of the instant invention is 1569 nucleotides in length. The Examiner agrees that SEQ ID NO:2 of Cases is 1509 nucleotides in length and SEQ ID NO:3 of the instant invention is 1569

nucleotides in length, as the sequence taught by Cases is missing approximately 60 nucleotides of the coding sequence of human ACAT-2 (see attached sequence alignment sheets). However, as Applicants have pointed out, Cases provides the coding sequence of the human ACAT-2 gene as SEQ ID NO:2. As Applicants have also pointed out, Cases does not teach a compound targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 that hybridizes with an inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40% or antisense oligonucleotides modified as specified by the present instant claims. However, it is the Examiner's position that using the sequence taught by Cases, and the generic teachings of Bennett and Fritz, one of ordinary skill in the art would expect success in designing an antisense nucleic acid targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 that hybridizes with an inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40% or antisense oligonucleotides modified as specified by the present instant claims. Applicants rebut this position and contend that there is no way for anyone of skill in the art to predict whether one may obtain any particular percentage of inhibition by prior knowledge of generic antisense technology coupled with a known target sequence. This is not found persuasive because as Applicants have pointed out, Applicants assignee has demonstrated repeatedly that one may investigate 80 or more oligonucleotides in attempts to identify a target site permitting inhibition [at a specific level] [for a specific gene]. This was demonstrated in the reference of Bennett where it was taught that using generic teachings, it would be expected that antisense oligonucleotides to a target gene will inhibit expression by at least 40% since a wide range of oligonucleotides are created with various inhibition capacities (see Tables 1 and 2). This

demonstration is further evident in other issued patents of Applicants' assignee, where it is taught that antisense oligonucleotides are designed to a target site and permit inhibition of gene expression [at a specific level] [for a specific target]. See for example, U.S. Patent Nos: 6,692,960 (Table 1), 6,692,959 (Table 1), 6,656,732 (Table 1), and 6,656,688 (Table 1). It is noted that in the instant case, the claims recite "by at least 40%". The coding region of the instant target is approximately 1500 nucleobases in length. It is the Examiners position that one of ordinary skill in the art could readily design antisense oligonucleotides targeting the coding region of the instant target and expect inhibition by at least 40%. This position is supported by the demonstrations illustrated in Table 1 of the issued Patents listed above. While one might find sequences that do not inhibit at all or that inhibit by considerably less than 40%, the prior art teaches that by targeting such a large region of a target gene (e.g. the coding region), one is **highly expected** to design antisense oligonucleotides that inhibits gene expression by at least 40% (see Bennett Tables 1 and 2 (art of record), U.S. Patent Nos: 6,692,960 (Table 1), 6,692,959 (Table 1), 6,656,732 (Table 1), or 6,656,688 (Table 1)). Further, and as argued in the previous Office Action, filed September 9, 2003, there is no evidence of record to show any such differences between the coding sequence of acyl CoA cholesterol acyltransferase-2 taught by Cases et al. (see Cases et al. SEQ ID NO: 2) and the coding sequence of acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3) of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to a coding region of acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3) that inhibits expression by at least 40%, since designing antisense oligonucleotides, with different inhibition capacities, to

known target genes, was well known in the art at the time of filing. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time of filing.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
March 12, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER